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Analysis of the dynamic energy flow associated with phagocytosis of bacteria

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Abstract

This paper treats the phenomenon of phagocytosis from the flow of energy point of view. Considerable efforts have been made towards elucidating the subject of phagocytosis in other fields of learning, but little has been said about the mechanical work that is done during phagocytosis. Phagocytosis without doubt is an interaction that involves the flow of energy. Energy equation model of phagocytosis is then presented in this paper to analyze the mechanical energy that is involved in the build-up of the engulfment of bacteria by the phagocytes. Data of the E Coli bacteria from published work was then applied to the solution of the energy equation. A borderline contact angle θ of 77.356° between the phagocyte and the bacteria at $\chi = 0$ was deduced in this work. It was shown that when $\theta < 77.356^\circ$, $\chi < 0$, engulfment is favoured and when $\theta > 77.356^\circ$, $\chi > 0$, engulfment is not favoured for E-coli. This condition is conceptually in line with ΔF_{NET} approach reported in the literature. Data of four different bacterial species were also used to plot the graphs of the engulfment parameter χ against contact angle θ which revealed that the more hydrophobic bacteria are easily phagocytized than the more hydrophilic ones.

Keywords: Phagocytosis, Contact angle, Engulfment, Bacteria, Phagocytes

1. Introduction

Phagocytosis is the process of engulfment and subsequent destruction and excretion of bacteria and other foreign particles by certain white blood cells called phagocytes. These special activities of the immune cells have attracted cross-disciplinary interest. Although considerable efforts have been devoted to elucidating the bio-chemical signaling pathways that control this process, the mechanical implementation of phagocytosis has received less attention [1]. Phagocytes are those white blood cells that provide the main defense against bacterial infections. They are found in all animals that ingest foreign substances and they form an important part of the innate immune system. There are two major types of phagocyte lineages: the polymorphonuclear granulocytes and mononuclear phagocytes. While the neutrophils comprise over 95% of the circulating polymorphonuclear granulocytes, the mononuclear phagocytes consist of circulating cells (the monocytes and macrophages) which reside in a variety of organs (example spleen, liver and lungs) where they display distinctive morphological features and perform diverse functions [2].

This paper will focus mainly on neutrophils as they are the most abundant type of phagocytes (about 70% of the white blood cell count in adult).

The innate immune system is the first line of defense in the human body against bacteria and other foreign particles. It is inherent in all animals and humans. At any time, there are about two billion phagocytes circulating through the body, regardless of whether an infection is present or not [3]. A phagocyte does not just “randomly encounter” a bacterium, but rather the phagocyte has receptors to detect the foreign component bodies like bacteria that are not normally present in the human body [4]. Even though this paper shall not concern itself with the taxonomy of phagocytosis but rather the dynamic energy flow associated with the engulfment process, a brief discussion of mechanism of phagocytosis is necessary. The mechanism of phagocytosis is not fully understood yet despite efforts from the 1970's. The first key insights leading to the popular zipper mechanism of phagocytosis were provided by Griffin and co-workers [13] [14]. The zipper mechanism has influenced recent works modeling dependence of engulfment on cell-membrane tension and ligand-receptor bond density. Questions, so far unanswered by the zipper mechanism are [15]; what the energetic requirements of the zipper mechanism are, what specific role actin polymerization plays in its progression during phagocytosis, and whether the zipper mechanism can explain the particle-shape dependence of phagocytosis. Ratchet-type mechanism has been suggested and supported with experimental observations in more recent times. In this mechanism, actin polymerization prevents the membrane from moving backwards like a ratchet [16] [17]. Tollis et al. [15] proposed a fully three-dimensional stochastic ratchet-like biophysical

model for the zipper mechanism of phagocytic engulfment. Actin polymerization makes ligand-receptor bonds effectively irreversible. They further investigated the role of actin and compared cup progression for the regular *active* zipper with a *passive* zipper model in which ligand-receptor binding remains specific and strong but *reversible* due to the absence of actin polymerization.

Phagocytosis without doubt is an interaction that involves changes in energy; so curiosity arises in this work to investigate the dynamic energy change associated with the neutrophil phagocytosis of bacteria. This paper hopes to propose and analyze the energy equation relevant to phagocytosis from a different point of view [5]. It is informative to note that although macrophages become the prevailing cell and remain in the infection site in high concentration for weeks, this work was however interested at what happens at the early part of host response to an infection; hence the choice of neutrophils. Also the choice of neutrophils was motivated by ready availability of simulation data. It is worthy of note that some authors choose Macrophages for their research but just like this work the following authors [16] [17] [18] [1] [19] equally chose neutrophils. Fig. 1 shows the five mechanical effectors involved in the engulfment of bacterium by a neutrophil. The five mechanical effectors are: adhesion, protrusion, contraction, cortical tension and viscoelastic resistance to shape changes [1]. According to the views of Lee et al. [1], adhesion provides bracing support during cell motion, enables phagocyte to hold on to their targets, and facilitates spreading of phagocytic cell over the target surface. The terms ‘protrusion’ and ‘contraction’ are used here as descriptors of outward and inward movement of parts of a motile cell, respectively. The cortical tension resists surface area expansion and maintains the spherical shape of passive cells in suspension. Finally, the viscosities of the cytoplasm, nucleus and cell cortex determine the rate of cell deformation for a given set of mechanical driving force.

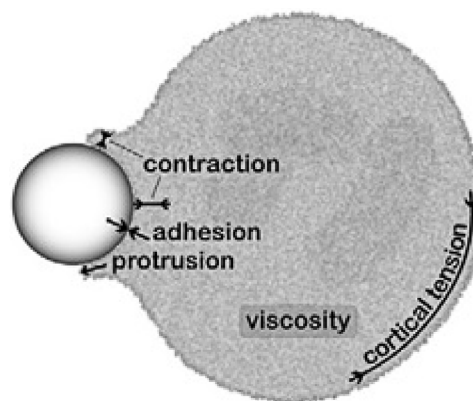


Fig. 1. Mechanical effectors of phagocytosis [1].

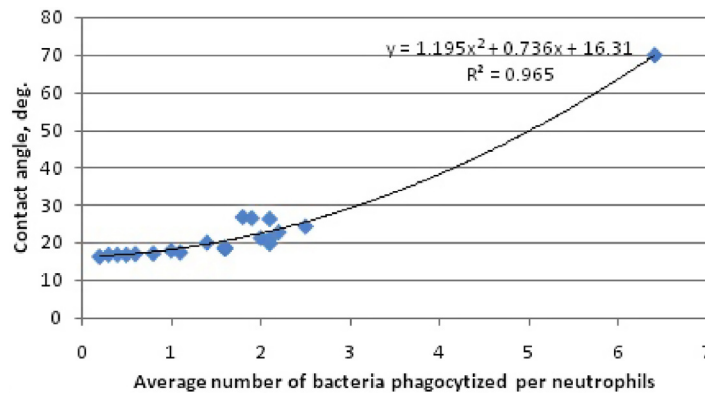


Fig. 2. The relationship between numbers of bacteria phagocytized and contact angle (with water) of bacteria [5].

2. Materials and methods

The notion that the phagocytic engulfment of bacteria by phagocytes such as neutrophils may be due to surface effects has been well known. This notion has equally been given a quantitative basis. The most important impact comes from the work of van Oss et al. [5] [6], who measured systematically and extensively contact angles on phagocytes and other cells as well as on various bacteria. The most immediate result of this work is the finding that hydrophobic bacteria are more readily engulfed by phagocytes than hydrophilic ones as shown in Fig. 2.

It becomes expedient that thermodynamic effect is necessary in the overall formulation of the mathematical model for phagocytosis of bacteria, as also stressed by van Oss et al. [7]. The process of ingestion of a particle, such as a free bacterium by a phagocyte generates a cell-bacterium interface as illustrated in Fig. 3.

This process is considered in this work from a thermodynamic point of view. At the interface, bacterium would not ‘like’ to go into the phagocyte for in so doing would be ‘killed’. Therefore, it will ‘resist’ going inside. The phagocyte has the responsibility to kill the bacterium, so will ‘like’ to ingest it. The change of energy of interaction occurs only when a phagocyte engages a bacterium as shown in Fig. 3. The energy of the interaction associated with build-up of engulfment by the phagocyte around the bacterium drawn from Fig. 3 by resolving the forces in some horizontal direction is given as [8], assuming an

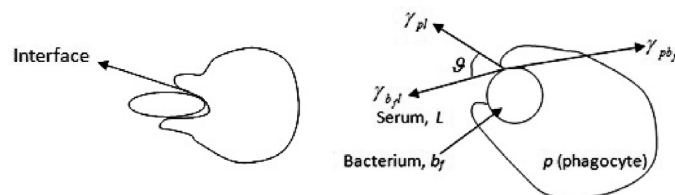


Fig. 3. Engulfment of a bacterium, b_f , by the phagocyte, p , all suspended in the serum, L [8].

area change of dA .

$$dE = (-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta) dA$$

We realize that the interaction area A between the phagocyte and the engaged bacterium will change during the engulfment dynamics from zero to the surface area of the bacterium A_b . If the engulfment interval is designated as t_{eng} then area rate of change dA/dt may be approximated with

$$\frac{dA}{dt} \cong \frac{A_b}{t_{eng}}$$

The energy equation thus becomes

$$\frac{dE}{dt} = (-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta) \frac{A_b}{t_{eng}}$$

Assuming that all bacterial deaths are due to surface phagocytosis then the above equation is multiplied with the population death of the free bacteria $\xi p b_f$ to give

$$\frac{dE}{dt} = \xi p b_f \frac{dE}{dt} = \xi \frac{A_b}{t_{eng}} (-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta) p b_f$$

The specific form of the proposed energy equation then reads

$$\frac{dE}{dt} = \xi \frac{v_{mem} A_b}{\pi r_b} (-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta) p(t) b_f(t) \quad (1)$$

where

E = Energy of interaction between the bacterium and the phagocyte

ξ = Free bacteria death rate

v_{mem} = Speed of advancement of membrane around the bacterium

A_b = Surface area of the engaged bacterium

r_b = Radius of the spherical shape of the engaged bacterium

γ_{pb_f} = The interfacial free energy between the phagocyte and free bacteria

$\gamma_{b_f l}$ = Interfacial free energy between free bacterium and serum

γ_{pL} = Interfacial free energy between the phagocyte and serum

$p(t)$ = Population of Phagocyte

$b_f(t)$ = Population of Free bacteria

ϑ = Contact angle between the phagocyte and the engaged bacterium

2.1. Solution of the energy equation

The engaged bacteria in the energy Eq. (1) are considered spherical with each of surface area $A_b = 4\pi r_b^2$. Eq. (1) then can take the form

$$\frac{dE}{dt} = 4\xi v_{mem} r_b \left(-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta \right) p(t) b_f(t) \quad (2)$$

The integration of Eq. (2) from initial time t_0 to time t is given by

$$E(t) = 4\xi v_{mem} r_b \left(-\gamma_{pb_f} + \gamma_{b_f l} + \gamma_{pL} \cos \vartheta \right) \int_{t_0}^t p(\tau) b_f(\tau) d\tau \quad (3)$$

The interfacial free energy γ_{pb_f} can be calculated using the Neumann equation of state [9]:

$$\gamma_{pb_f} = \frac{\left(\sqrt{\gamma_{pv}} - \sqrt{\gamma_{b_f v}} \right)^2}{1 - 0.015 \sqrt{\gamma_{pv} \gamma_{b_f v}}} \quad (4)$$

where γ_{iv} is the surface free energy of given species, i, measured in air and given in Table 1.

Making use of the Neumann equation of state gives

$$E(t) = 4\xi v_{mem} r_b \left(-\frac{\left(\gamma_{pv}^{0.5} - \gamma_{b_f v}^{0.5} \right)^2}{1 - 0.015 \left(\gamma_{pv} \gamma_{b_f v} \right)^{0.5}} + \frac{\left(\gamma_{b_f v}^{0.5} - \gamma_{lv}^{0.5} \right)^2}{1 - 0.015 \left(\gamma_{b_f v} \gamma_{lv} \right)^{0.5}} + \frac{\left(\gamma_{pv}^{0.5} - \gamma_{lv}^{0.5} \right)^2}{1 - 0.015 \left(\gamma_{pv} \gamma_{lv} \right)^{0.5}} \cos \vartheta \right) \int_{t_0}^t p(\tau) b_f(\tau) d\tau \quad (5)$$

Eq. (5) can be written in the form

$$E(t) = CD(t) \quad (6)$$

where

$$D(t) = \int_{t_0}^t p(\tau) b_f(\tau) d\tau \quad (7)$$

Table 1. Thermodynamic data [5] [6].

Material	Surface free energy, γ_{iv} , mJ/m ²	Contact angle, deg. (with water)	Reference
Serum	70.2		[6]
Bacteria			
E-coli	69.7	17.2	[10]
S-aureus	69.1	18.7	„
S-epidermidus	67.1	24.5	„
L-monocytogenes	66.3	26.5	„
Human granulocytes	69.1		[5]
Human neutrophils	69.0	18	[11]

and

$$C = 4\xi v_{mem} r_b \left(-\frac{(\gamma_{pv}^{0.5} - \gamma_{bfv}^{0.5})^2}{1 - 0.015(\gamma_{pv}\gamma_{bfv})^{0.5}} + \frac{(\gamma_{bfv}^{0.5} - \gamma_{lv}^{0.5})^2}{1 - 0.015(\gamma_{bfv}\gamma_{lv})^{0.5}} + \frac{(\gamma_{pv}^{0.5} - \gamma_{lv}^{0.5})^2}{1 - 0.015(\gamma_{pv}\gamma_{lv})^{0.5}} \cos\vartheta \right) \quad (8)$$

C has the unit of energy and D of s^{-1} . $\xi = \text{mL/phagocyte cell/hr}$; $r_b = m$,
 $v = m/s$.

Eq. (8) can also be written in the form

$$\chi = \frac{C}{v_{mem} r_b} = 4\xi \left(-\frac{(\gamma_{pv}^{0.5} - \gamma_{bfv}^{0.5})^2}{1 - 0.015(\gamma_{pv}\gamma_{bfv})^{0.5}} + \frac{(\gamma_{bfv}^{0.5} - \gamma_{lv}^{0.5})^2}{1 - 0.015(\gamma_{bfv}\gamma_{lv})^{0.5}} + \frac{(\gamma_{pv}^{0.5} - \gamma_{lv}^{0.5})^2}{1 - 0.015(\gamma_{pv}\gamma_{lv})^{0.5}} \cos\vartheta \right) \quad (9)$$

where χ has the unit of $\frac{\text{mL}}{\text{phagocyte cell.hr}} \times \frac{\text{mJ}}{\text{m}^2}$

The energy history of phagocytosis can only be estimated numerically when numerical solutions of both $p(t)$ and $b_f(t)$ are inserted in the discretized form of Eq. (5). The discrete integration schemes are then solved recursively to generate the numerical discrete time history $E(t)$. The details of these are seen in the work of Okpala [8]. It is seen that sign of the phagocytotic energy is dictated by sign of the new parameter χ meaning that negative χ suggests exothermic engulfment process (occurring by surface thermodynamic effects alone) while positive χ suggests endothermic engulfment process can only occur when aided. The new parameter χ is called “engulfment parameter” in this work. For the purposes of the discussion on this paper, the analysis shall be based on Eq. (9).

3. Results

Suppose the Human neutrophils are engulfing the E-coli bacteria, the parameters of C as sourced from Table 1 become

$$\gamma_{pv} = 69\text{mJ/m}^2$$

$$\gamma_{bfv} = 69.7\text{mJ/m}^2$$

$$\gamma_{lv} = 70.2\text{mJ/m}^2$$

ξ has been set to biological plausible value of $1.0 \times 10^{-7} \text{ mL/(phagocyte cell)/hr}$ [3]. Inserting the above numerical values into Eq. (9) gives

$$\chi = 1.0302 \times 10^{-8} - 4.7064 \times 10^{-8} \cos\vartheta \quad (10)$$

It is seen from Eq. (10) that $\chi = 0$ when $\vartheta = \cos^{-1}(1.0302/4.7064)$
 $= 1.3501\text{rad} = 77.356^\circ$. A plot of χ against ϑ is presented in Fig. 4 below. It is seen from Fig. 4 that some typical values of χ at selected values of ϑ are as

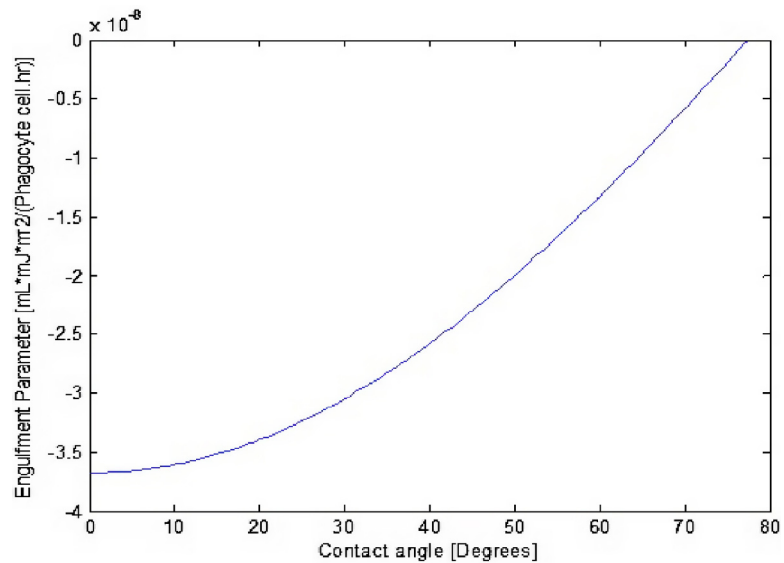


Fig. 4. A graphical variation of engulfment parameter χ with contact angle θ .

given in Table 2 below. For more detailed look at χ a plot of a broad range is shown in Fig. 5.

Since data exist for other types of bacteria (Table 1), it will be interesting to carry out computations using Eq. (9) for these bacterial species. Their graphs will then be plotted on the same axis with of E-Coli bacteria for further discussion. Suppose the Human neutrophils are engulfing the S-aureus, the S-epidermidus, and the L-monocytogenes bacteria; the parameters of C as sourced from Table 1 become; $\gamma_{pv} = 69 \text{ mJ}/\text{m}^2$, $\gamma_{b_{fv}} = 69.1 \text{ mJ}/\text{m}^2$ (S-aureus), $\gamma_{b_{fv}} = 67.1 \text{ mJ}/\text{m}^2$ (S-epidermidus), $\gamma_{b_{fv}} = 66.3 \text{ mJ}/\text{m}^2$ (L-monocytogenes) and $\gamma_{lv} = 70.2 \text{ mJ}/\text{m}^2$. Inserting the above values into Eq. (9) gives

$$\chi = -3.8445 \times 10^{-8} - 4.7064 \times 10^{-8} \cos \theta \quad (14)$$

(for S-aureus bacteria)

$$\chi = -2.1789 \times 10^{-7} - 4.7064 \times 10^{-8} \cos \theta \quad (15)$$

(for S-epidermidus bacteria)

Table 2. Some typical values of χ at selected values of θ .

θ [degrees]	$\chi \left[\frac{\text{mL}}{\text{phagocyte cell hr}} \times \frac{\text{mJ}}{\text{m}^2} \right]$
0	-3.6762×10^{-8}
19.339	-3.4106×10^{-8}
38.678	-2.6439×10^{-8}
58.017	-1.4626×10^{-8}
77.356	0

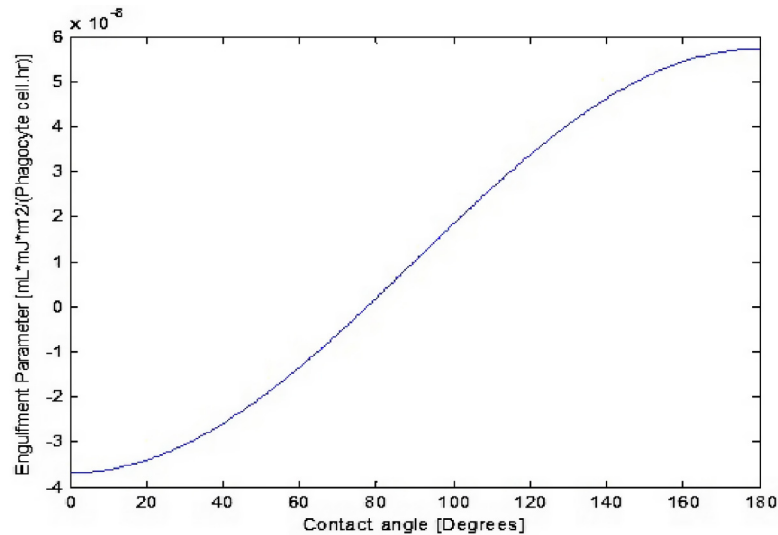


Fig. 5. A broader graphical variation of engulfment parameter χ with contact angle θ .

$$\chi = -2.1455 \times 10^{-7} - 4.7064 \times 10^{-8} \cos \theta \quad (16)$$

(for L-monocytogenes bacteria)

A plot of χ against θ is presented in Fig. 7 below for Eqs. (10), (14), (15) and (16).

4. Discussion

The negative values of χ suggest that phagocytosis will take place by surface thermodynamics alone with the release of energy (exothermic process). The positive values of χ on the other hand suggest that engulfment will not take place unaided. From Fig. 5 above, one can easily observe that χ turns positive at an angle θ greater than 77.356° . Beyond this region (endothermic process), engulfment will not take place unaided. Integration of the proposed energy equation was done numerically and it was seen that the result would not offer in-depth qualitative discussion of phagocytosis. A parameter that potentially offers much broader qualitative discussion than the energy equation itself is the engulfment parameter χ , given more generally in Eq. (9) and more specifically in Eq. (10) for engulfment of E-coli bacteria. It is known that phagocytosis will take place when free surface energy of engulfment is negative (exothermic). On the other hand, if the free surface energy of engulfment is positive (endothermic), then phagocytosis will not occur. For it to occur, an external force will be required to force the bacterium inside the phagocyte. Cell density is always positive for positive time. This means that the integral in Eq. (3) is always positive since negative time is not feasible in this work. It is then seen that the energy of engulfment being positive or negative is entirely dictated by the sign of χ and that the sign of χ is entirely determined by the surface energy

properties; γ_{pv} , γ_{bfv} , γ_{lv} and ϑ . It is noted that the Thermodynamic condition [7] [11] [12] for particle engulfment is that the net change in free energy, ΔF_{NET} for the process of particle engulfment is less than zero, i.e., if

$$\Delta F_{NET} < 0 \quad (11)$$

There will be particle engulfment, and if it is larger than zero, i.e., if

$$\Delta F_{NET} > 0 \quad (12)$$

There will be particle rejection, and

$$\Delta F_{NET} = -\gamma_{pb} + \gamma_{pi} \quad (13)$$

The engulfment parameter χ can be understood in line with the ΔF_{NET} condition. The Thermodynamic condition for particle engulfment as expressed by ΔF_{NET} is similar to that expressed by χ as discussed above. Since the surface energies; γ_{pv} , γ_{bfv} and γ_{lv} are normally fixed, the angle ϑ is studied in what follows to determine its effect on readiness of engulfment to occur. The rationality of using the engulfment parameter χ as a criterion of whether or not engulfment will take place is demonstrated by the respective sketches of the borderline case for E Coli bacteria ($\vartheta = 77.356$, $\chi = 0$), the case where engulfment is favoured ($\vartheta < 77.356$, $\chi < 0$) and the case where engulfment is not favoured ($\vartheta > 77.356$, $\chi > 0$).

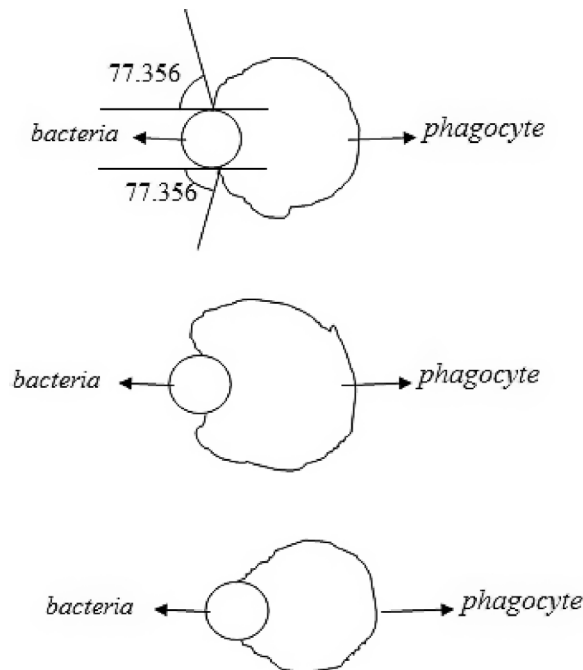


Fig. 6. The engulfment parameter χ as a criterion of whether or not engulfment will take place is demonstrated by respective sketches of (a) the borderline case ($\vartheta = 77.356$, $\chi = 0$), (b) the case where engulfment is favoured ($\vartheta < 77.356$, $\chi < 0$) and (c) the case where engulfment is not favoured ($\vartheta > 77.356$, $\chi > 0$).

($\vartheta > 77.356^\circ$, $\chi > 0$) in Fig. 6a–c. It is seen that configuration of each sketch agrees with this assertion.

It is seen from Eq. (14) that $\chi = 0$ when $\vartheta = \cos^{-1}(-3.8445/4.7064) = 144.77^\circ$ for the S-aureus bacteria. From Fig. 7 above, one can easily observe that χ turns positive at an angle ϑ greater than 144.77° for the S-aureus bacteria. Beyond this region (endothermic process), engulfment will not take place unaided. The rationality of using the engulfment parameter χ as a criterion of whether or not engulfment will take place can also be applied to the S-aureus bacteria being demonstrated by the borderline case for S-aureus bacteria ($\vartheta = 144.77^\circ$, $\chi = 0$), the case where engulfment is favoured ($\vartheta < 144.77^\circ$, $\chi < 0$) and the case where engulfment is not favoured ($\vartheta > 144.77^\circ$, $\chi > 0$). A close observation on Fig. 7 reveals that S-epidermidus and L-monocytogenes bacteria demonstrate persistent negative values of χ , and thus are engulfed at all angles. This could be stemming from the fact that their contact angles are relatively higher (see Table 1), thereby causing low interfacial tension between the bacteria and serum creating a favourable condition for engulfment. Fig. 7 confirms the fact that the more hydrophobic bacteria get easily phagocytized than the more hydrophilic bacteria as shown also in Fig. 1 and also reported by Absalom et al. [5].

The following points are made about the rational and application of this work. The extent of the coverage of the surface of the bacterium by the neutrophil to guarantee engulfment has been estimated via analysis of engulfment energy. It

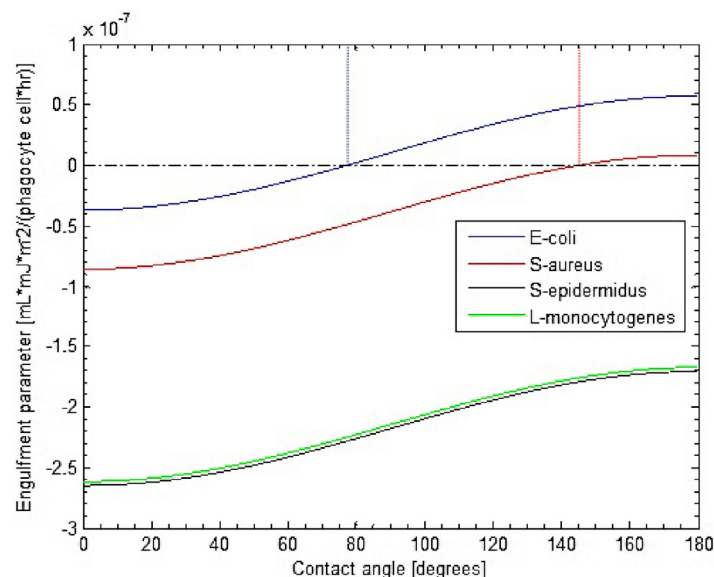


Fig. 7. A broader graphical variation of engulfment parameter χ with contact angle ϑ for four different bacterial species. The blue vertical line indicates the borderline contact angle for E-coli while the red vertical line indicates the borderline contact angle for S-aureus.

should be recalled that a point is made earlier in this work; The negative values of χ suggest that phagocytosis can take place by surface thermodynamics alone with the release of energy (exothermic process). This energy release could be one of the reasons why sometimes the human body temperature rises when battling with pathogens. The knowledge of threshold values of contact angles for engulfment could aid the Pharmaceutical industry in design of the drugs that will facilitate phagocytic engulfment of the bacteria by the neutrophils.

5. Conclusion

An energy equation of phagocytosis was derived in this work to demonstrate the role of surface thermodynamics in the neutrophils phagocytosis of bacteria. The solution of the presented energy equation was written in integrated form using the convolution integral as seen in Eq. (3) but the complete analytical solution could not be generated because of presence of terms $p(t)$ and $b_f(t)$ that do not have pure analytical forms in the integrand. This paper was however limited to the analysis of part of the energy equation. A new parameter χ , the engulfment parameter, that has value and sign entirely determined by the surface energy properties $\gamma_{pv}, \gamma_{b_{fv}}, \gamma_{lv}$ and θ , was identified in this work to be a valid criterion for engulfment similar to that predicted by the energy equation of Neumann [5] [7]. The results confirm, as found by others [5] [7], that the more hydrophobic bacteria are more easily phagocytized.

Declarations

Author contribution statement

Sam Omenyi, Paul Okpala, Chigbogu Ozoegwu: Conceived the research idea and designed the experiments; Wrote the paper.

Chigbogu Ozoegwu: Conceived and generated the energy flow model; Analyzed and interpreted the results.

Paul Okpala, Chigbogu Ozoegwu, Chinonso Achebe: Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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